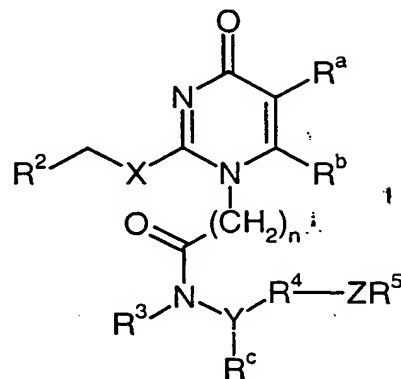


What is claimed is:

1. A compound of formula (I):



in which:

$R^a$  is hydrogen, halogen,  $C_{(1-3)}$ alkyl,  $C_{(1-3)}$ alkoxy, hydroxy $C_{(1-3)}$ alkyl,  $C_{(1-3)}$ alkylthio,  $C_{(1-3)}$ alkylsulphanyl, amino $C_{(1-3)}$ alkyl, mono- or di- $C_{(1-3)}$ alkylamino $C_{(1-3)}$ alkyl,  $C_{(1-3)}$ alkylcarbonylamino $C_{(1-3)}$ alkyl,  $C_{(1-3)}$ alkoxy $C_{(1-3)}$ alkylcarbonylamino $C_{(1-3)}$ alkyl,  $C_{(1-3)}$ alkylsulphonylamino $C_{(1-3)}$ alkyl,  $C_{(1-3)}$ alkylcarboxy, or  $C_{(1-3)}$ alkylcarboxy $C_{(1-3)}$ alkyl;

$R^b$  is hydrogen, halogen,  $C_{(1-3)}$ alkyl, or hydroxy $C_{(1-3)}$ alkyl, with the proviso that  $R^a$  and  $R^b$  are not simultaneously each hydrogen; or

$R^a$  and  $R^b$  together are  $(CH_2)_n$  where  $n$  is 3 or 4, to form, with the pyrimidine ring carbon atoms to which they are attached a fused 5- or 6-membered carbocyclic ring; or

$R^a$  and  $R^b$  together with the pyrimidine ring carbon atoms to which they are attached form a fused benzo or heteroaryl ring unsubstituted or substituted by 1, 2, 3 or 4 substituents which may be the same or different selected from the group consisting of halogen,  $C_{(1-4)}$ alkyl, cyano,  $C_{(1-4)}$ alkoxy or  $C_{(1-4)}$ alkylthio, and mono to perfluoro- $C_{(1-4)}$ alkyl);

$R^c$  is hydrogen or  $C_{(1-3)}$ alkyl;

$R^2$  is an aryl or heteroaryl group, unsubstituted or substituted by 1, 2, 3 or 4 substituents which may be the same or different selected from the group consisting

of C<sub>(1-18)</sub>alkyl, C<sub>(1-18)</sub>alkoxy, C<sub>(1-18)</sub>alkylthio, arylC<sub>(1-18)</sub>alkoxy, hydroxy, halogen, CN, COR<sup>6</sup>, carboxy, COOR<sup>6</sup>, NR<sup>6</sup>COR<sup>7</sup>, CONR<sup>8</sup>R<sup>9</sup>, SO<sub>2</sub>NR<sup>8</sup>R<sup>9</sup>, NR<sup>6</sup>SO<sub>2</sub>R<sup>7</sup>, NR<sup>8</sup>R<sup>9</sup>, mono to perfluoro-C<sub>(1-4)</sub>alkyl, mono to perfluoro-C<sub>(1-4)</sub>alkoxyaryl, and arylC<sub>(1-4)</sub>alkyl;

5           R<sup>3</sup> is hydrogen, C<sub>(1-6)</sub>alkyl which may be unsubstituted or substituted by 1, 2 or 3 substituents selected from the group consisting of hydroxy, halogen, OR<sup>6</sup>, COR<sup>6</sup>, carboxy, COOR<sup>6</sup>, CONR<sup>8</sup>R<sup>9</sup>, NR<sup>8</sup>R<sup>9</sup>, NR<sup>8</sup>COR<sup>9</sup>, mono- or di-(hydroxyC<sub>(1-6)</sub>alkyl)amino and N-hydroxyC<sub>(1-6)</sub>alkyl-N-C<sub>(1-6)</sub>alkylamino; or

10           R<sup>3</sup> is Het-C<sub>(0-4)</sub>alkyl in which Het is a 5- to 7- membered heterocyclyl ring comprising N and optionally O or S, bonded through a carbon ring atom and in which N is unsubstituted or substituted by COR<sup>6</sup>, COOR<sup>6</sup>, CONR<sup>8</sup>R<sup>9</sup>, or C<sub>(1-6)</sub>alkyl unsubstituted or substituted by 1, 2 or 3 substituents selected from the group consisting of hydroxy, halogen, OR<sup>6</sup>, COR<sup>6</sup>, carboxy, COOR<sup>6</sup>, CONR<sup>8</sup>R<sup>9</sup> and NR<sup>8</sup>R<sup>9</sup>;

15           R<sup>4</sup> is an aryl or a heteroaryl ring unsubstituted or substituted by 1, 2, 3 or 4 substituents which may be the same or different selected from the group consisting of C<sub>(1-18)</sub>alkyl, C<sub>(1-18)</sub>alkoxy, C<sub>(1-18)</sub>alkylthio, arylC<sub>(1-18)</sub>alkoxy, hydroxy, halogen, CN, COR<sup>6</sup>, carboxy, COOR<sup>6</sup>, NR<sup>6</sup>COR<sup>7</sup>, CONR<sup>8</sup>R<sup>9</sup>, SO<sub>2</sub>NR<sup>8</sup>R<sup>9</sup>, NR<sup>6</sup>SO<sub>2</sub>R<sup>7</sup>, NR<sup>8</sup>R<sup>9</sup>, mono to perfluoro-C<sub>(1-4)</sub>alkyl and mono to perfluoro-C<sub>(1-4)</sub>alkoxy;

20           R<sup>5</sup> is an aryl or heteroaryl ring which is unsubstituted or substituted by 1, 2, 3 or 4 substituents which may be the same or different selected from the group consisting of C<sub>(1-18)</sub>alkyl, C<sub>(1-18)</sub>alkoxy, C<sub>(1-18)</sub>alkylthio, arylC<sub>(1-18)</sub>alkoxy, hydroxy, halogen, CN, COR<sup>6</sup>, carboxy, COOR<sup>6</sup>, CONR<sup>8</sup>R<sup>9</sup>, NR<sup>6</sup>COR<sup>7</sup>, SO<sub>2</sub>NR<sup>8</sup>R<sup>9</sup>, NR<sup>6</sup>SO<sub>2</sub>R<sup>7</sup>, NR<sup>8</sup>R<sup>9</sup>, mono to perfluoro-C<sub>(1-4)</sub>alkyl and mono to perfluoro-C<sub>(1-4)</sub>alkoxy;

          R<sup>6</sup> and R<sup>7</sup> are independently hydrogen or C<sub>(1-20)</sub>alkyl;

          R<sup>8</sup> and R<sup>9</sup> may be the same or different and are selected from the group consisting of hydrogen and C<sub>(1-12)</sub>alkyl; or

30           R<sup>8</sup> and R<sup>9</sup> together with the nitrogen to which they are attached form a 5- to 7 membered ring optionally containing one or more further heteroatoms which are oxygen, nitrogen or sulphur, and is unsubstituted or substituted by one or two

substituents selected from the group consisting of hydroxy, oxo,  $C_{(1-4)}$ alkyl,  $C_{(1-4)}$ alkylCO, aryl, and aralkyl; or

$R^8$  and  $R^9$  may be the same or different and are selected from the group consisting of  $CH_2R^{10}$  and  $CHR^{11}CO_2H$ , or a salt thereof;

5  $R^{10}$  is  $COOH$  or a salt thereof,  $COOR^{12}$ ,  $CONR^6R^7$ ,  $CN$ ,  $CH_2OH$  or  $CH_2OR^6$ ;

$R^{11}$  is an amino acid side chain;

$R^{12}$  is  $C_{(1-4)}$ alkyl or a pharmaceutically acceptable *in vivo* hydrolysable ester group;

10  $n$  is 1 to 4;

$X$  is O or S;

$Y$  is  $(CH_2)_p(O)_q$  in which  $p$  is 1, 2 or 3 and  $q$  is 0 or  $p$  is 2 or 3 and  $q$  is 1;

and

$Z$  is O or a bond.

15 2. A compound as claimed in claim 1 in which  $R^a$  is chloro, bromo, methyl, ethyl, *n*-propyl, methoxy, hydroxymethyl, hydroxyethyl, methylthio, methylsulphonyl, aminoethyl, dimethylaminomethyl, acetylaminoethyl, 2-(methoxyacetamido)ethyl, mesylaminoethyl, ethylcarboxy, methanesulfonamidoethyl, (methoxyacetamido)ethyl or iso-propylcarboxymethyl.

20 3. A compound as claimed in claim 1 in which  $R^b$  is hydrogen or methyl.

4. A compound as claimed in claim 1 in which  $R^a$  and  $R^b$  together with the pyrimidine ring carbon atoms to which they are attached form a fused 5-membered carbocyclic ring or a fused benzo or heteroaryl ring selected from the group consisting of benzo, pyrido and thieno.

25 5. A compound as claimed in claim 1 in which  $R^c$  is hydrogen or methyl.

6. A compound as claimed in claim 1 in which  $X$  is S.

7. A compound as claimed in claim 1 in which  $Y$  is  $CH_2$ .

8. A compound as claimed in claim 1 in which  $Z$  is a direct bond.

9. A compound as claimed in claim 1 in which  $R^2$  is an aryl group,  
30 unsubstituted or substituted by 1, 2, 3 or 4 substituents which are the same or different and are selected from the group consisting of  $C_{(1-6)}$ alkyl,  $C_{(1-6)}$ alkoxy,

C<sub>(1-6)</sub>alkylthio, hydroxy, halogen, CN, mono to perfluoro-C<sub>(1-4)</sub>alkyl, mono to perfluoro-C<sub>(1-4)</sub>alkoxyaryl, and arylC<sub>(1-4)</sub>alkyl.

10. A compound as claimed in claim 1 in which R<sup>2</sup> is phenyl, unsubstituted or substituted by halogen.

5 11. A compound as claimed in claim 1 in which R<sup>2</sup> is phenyl optionally substituted by one to three fluorine atoms.

12. A compound as claimed in claim 1 in which R<sup>3</sup> is C<sub>(1-3)</sub>alkyl substituted by a substituent which is NR<sup>8</sup>R<sup>9</sup>; or R<sup>3</sup> is Het-C<sub>(0-2)</sub>alkyl in which Het is a 5- to 7- membered heterocyclyl ring comprising N and in which N is  
10 unsubstituted or substituted by C<sub>(1-6)</sub>alkyl.

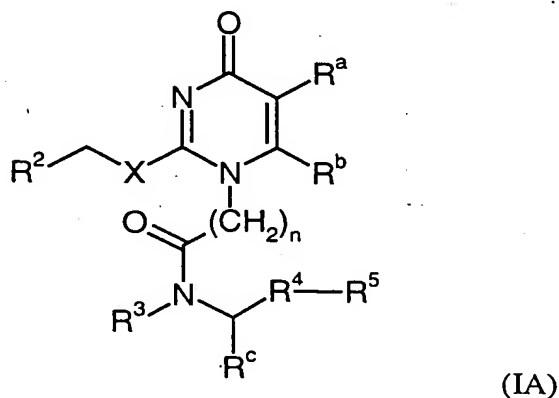
13. A compound as claimed in claim 1 in which R<sup>3</sup> is 2-(diethylamino)ethyl.

14. A compound as claimed in claim 1 in which R<sup>4</sup> is phenyl.

15 15. A compound as claimed in claim 1 in which R<sup>5</sup> is phenyl substituted by trifluoromethyl.

16. A compound as claimed in claim 1 in which R<sup>4</sup> and R<sup>5</sup> together form a 4-(4-trifluoromethylphenyl)phenyl moiety.

17. A compound of the formula (IA):



20

in which:

R<sup>a</sup> is hydrogen, halogen, C<sub>(1-3)</sub>alkyl, C<sub>(1-3)</sub>alkoxy, hydroxyC<sub>(1-3)</sub>alkyl, C<sub>(1-3)</sub>alkylthio, C<sub>(1-3)</sub>alkylsulphinyl, aminoC<sub>(1-3)</sub>alkyl, mono- or di-C<sub>(1-3)</sub>alkylaminoC<sub>(1-3)</sub>alkyl, C<sub>(1-3)</sub>alkylcarbonylaminoC<sub>(1-3)</sub>alkyl,  
25 C<sub>(1-3)</sub>alkoxyC<sub>(1-3)</sub>alkylcarbonylaminoC<sub>(1-3)</sub>alkyl,

C<sub>(1-3)</sub>alkylsulphonylaminoC<sub>(1-3)</sub>alkyl, C<sub>(1-3)</sub>alkylcarboxy, or  
C<sub>(1-3)</sub>alkylcarboxyC<sub>(1-3)</sub>alkyl;

R<sup>b</sup> is hydrogen, halogen, C<sub>(1-3)</sub>alkyl, or hydroxyC<sub>(1-3)</sub>alkyl, with the proviso that R<sup>a</sup> and R<sup>b</sup> are not simultaneously each hydrogen; or

- 5 R<sup>a</sup> and R<sup>b</sup> together are (CH<sub>2</sub>)<sub>n</sub> where n is 3 or 4, to form, with the pyrimidine ring carbon atoms to which they are attached a fused 5- or 6-membered carbocyclic ring; or

- 10 R<sup>a</sup> and R<sup>b</sup> together with the pyrimidine ring carbon atoms to which they are attached form a fused benzo or heteroaryl ring unsubstituted or substituted by 1, 2, 3 or 4 substituents which may be the same or different selected from the group consisting of halogen, C<sub>(1-4)</sub>alkyl, cyano, C<sub>(1-4)</sub>alkoxy or C<sub>(1-4)</sub>alkylthio, and mono to perfluoro-C<sub>(1-4)</sub>alkyl);

R<sup>c</sup> is hydrogen or C<sub>(1-3)</sub>alkyl;

- 15 R<sup>2</sup> is an aryl or heteroaryl group, unsubstituted or substituted by 1, 2, 3 or 4 substituents which may be the same or different selected from the group consisting C<sub>(1-18)</sub>alkyl, C<sub>(1-18)</sub>alkoxy, C<sub>(1-18)</sub>alkylthio, arylC<sub>(1-18)</sub>alkoxy, hydroxy, halogen, CN, COR<sup>6</sup>, carboxy, COOR<sup>6</sup>, NR<sup>6</sup>COR<sup>7</sup>, CONR<sup>8</sup>R<sup>9</sup>, SO<sub>2</sub>NR<sup>8</sup>R<sup>9</sup>, NR<sup>6</sup>SO<sub>2</sub>R<sup>7</sup>, NR<sup>8</sup>R<sup>9</sup>, mono to perfluoro-C<sub>(1-4)</sub>alkyl, mono to perfluoro-C<sub>(1-4)</sub>alkoxyaryl, and arylC<sub>(1-4)</sub>alkyl;

- 20 R<sup>3</sup> is hydrogen, C<sub>(1-6)</sub>alkyl which may be unsubstituted or substituted by 1, 2 or 3 substituents selected from the group consisting of hydroxy, halogen, OR<sup>6</sup>, COR<sup>6</sup>, carboxy, COOR<sup>6</sup>, CONR<sup>8</sup>R<sup>9</sup>, NR<sup>8</sup>R<sup>9</sup>, NR<sup>8</sup>COR<sup>9</sup>, mono- or di-(hydroxyC<sub>(1-6)</sub>alkyl)amino and N-hydroxyC<sub>(1-6)</sub>alkyl-N-C<sub>(1-6)</sub>alkylamino; or

- 25 R<sup>3</sup> is Het-C<sub>(0-4)</sub>alkyl in which Het is a 5- to 7- membered heterocyclyl ring comprising N and optionally O or S, bonded through a carbon ring atom and in which N is unsubstituted or substituted by COR<sup>6</sup>, COOR<sup>6</sup>, CONR<sup>8</sup>R<sup>9</sup>; or C<sub>(1-6)</sub>alkyl unsubstituted or substituted by 1, 2 or 3 substituents selected from the group consisting of hydroxy, halogen, OR<sup>6</sup>, COR<sup>6</sup>, carboxy, COOR<sup>6</sup>, CONR<sup>8</sup>R<sup>9</sup> and NR<sup>8</sup>R<sup>9</sup>;

- 30 R<sup>4</sup> is an aryl or a heteroaryl ring optionally substituted by 1, 2, 3 or 4 substituents which may be the same or different selected from the group consisting of C<sub>(1-18)</sub>alkyl, C<sub>(1-18)</sub>alkoxy, C<sub>(1-18)</sub>alkylthio, arylC<sub>(1-18)</sub>alkoxy, hydroxy,

halogen, CN, COR<sup>6</sup>, carboxy, COOR<sup>6</sup>, NR<sup>6</sup>COR<sup>7</sup>, CONR<sup>8</sup>R<sup>9</sup>, SO<sub>2</sub>NR<sup>8</sup>R<sup>9</sup>, NR<sup>6</sup>SO<sub>2</sub>R<sup>7</sup>, NR<sup>8</sup>R<sup>9</sup>, mono to perfluoro-C<sub>(1-4)</sub>alkyl and mono to perfluoro-C<sub>(1-4)</sub>alkoxy;

5 R<sup>5</sup> is an aryl or heteroaryl ring which is unsubstituted or substituted by 1, 2, 3 or 4 substituents which may be the same or different selected from the group consisting of C<sub>(1-18)</sub>alkyl, C<sub>(1-18)</sub>alkoxy, C<sub>(1-18)</sub>alkylthio, arylC<sub>(1-18)</sub>alkoxy, hydroxy, halogen, CN, COR<sup>6</sup>, carboxy, COOR<sup>6</sup>, CONR<sup>8</sup>R<sup>9</sup>, NR<sup>6</sup>COR<sup>7</sup>, SO<sub>2</sub>NR<sup>8</sup>R<sup>9</sup>, NR<sup>6</sup>SO<sub>2</sub>R<sup>7</sup>, NR<sup>8</sup>R<sup>9</sup>, mono to perfluoro-C<sub>(1-4)</sub>alkyl and mono to perfluoro-C<sub>(1-4)</sub>alkoxy;

10 R<sup>6</sup> and R<sup>7</sup> are independently hydrogen or C<sub>(1-20)</sub>alkyl;

R<sup>8</sup> and R<sup>9</sup> may be the same or different and are selected from the group consisting of hydrogen and C<sub>(1-12)</sub>alkyl; or

15 R<sup>8</sup> and R<sup>9</sup> together with the nitrogen to which they are attached form a 5- to 7 membered ring optionally containing one or more further heteroatoms which are oxygen, nitrogen or sulphur, and is unsubstituted or substituted by one or two substituents selected from the group consisting of hydroxy, oxo, C<sub>(1-4)</sub>alkyl, C<sub>(1-4)</sub>alkylCO, aryl, and aralkyl; or

R<sup>8</sup> and R<sup>9</sup> may be the same or different and are selected from the group consisting of CH<sub>2</sub>R<sup>10</sup> and CHR<sup>11</sup>CO<sub>2</sub>H, or a salt thereof;

20 R<sup>10</sup> is COOH or a salt thereof, COOR<sup>12</sup>, CONR<sup>6</sup>R<sup>7</sup>, CN, CH<sub>2</sub>OH or CH<sub>2</sub>OR<sup>6</sup>;

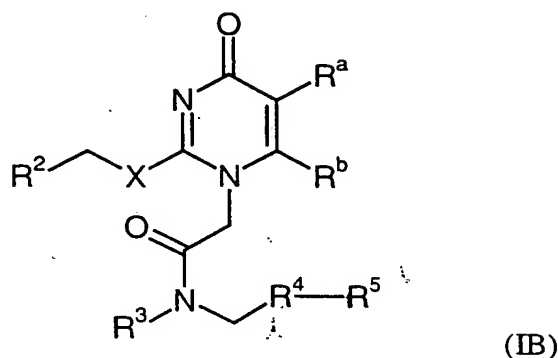
R<sup>11</sup> is an amino acid side chain;

R<sup>12</sup> is C<sub>(1-4)</sub>alkyl or a pharmaceutically acceptable *in vivo* hydrolysable ester group;

25 n is 1 to 4; and

X is O or S.

18. A compound of the formula (IB):



in which:

- 5             $R^a$  and  $R^b$  together with the pyrimidine ring carbon atoms to which they are attached form a fused 5-membered carbocyclic ring;

$R^2CH_2X$  is 4-fluorobenzylthio;

$R^3$  is  $C_{(1-3)}$ alkyl substituted by  $NR^8R^9$ ; or

- 10            $R^3$  is Het- $C_{(0-2)}$ alkyl in which Het is a 5- to 7- membered heterocyclyl ring comprising N and in which N is unsubstituted or substituted by  $C_{(1-6)}$ alkyl;

$R^4$  and  $R^5$  form a 4-(4-trifluoromethylphenyl)phenyl moiety;

$R^8$  and  $R^9$  which may be the same or different are selected from the group consisting of hydrogen, or  $C_{(1-6)}$ alkyl); and

X is S.

- 15           19. A compound as claimed in claim 1 which is:

1-(N-(2-(diethylamino)ethyl)-N-(4-(4-trifluoromethylphenyl)benzyl)aminocarbonylmethyl)-2-(4-fluorobenzyl)thio-5-ethylpyrimidin-4-one;

1-(N-(2-(diethylamino)ethyl)-N-(2-(4-trifluoromethylphenyl)pyrid-5-yl-methyl)aminocarbonylmethyl)-2-(4-fluorobenzyl)thio-5-ethylpyrimidin-4-one; 1-

- 20           (N-(2-(diethylamino)ethyl)-N-(4-(4-trifluoromethylphenyl)benzyl)-aminocarbonylmethyl)-2-(4-fluorobenzyl)thio-5,6-trimethylenepyrimidin-4-one; 1-(N-(2-(diethylamino)ethyl)-N-(2-(4-trifluoromethylphenyl)pyrid-5-yl-methyl)aminocarbonylmethyl)-2-(4-fluorobenzyl)thio-5,6-trimethylenepyrimidin-4-one;

1-(N-(2-(diethylamino)ethyl)-N-(2-(4-trifluoromethylphenyl)pyrimid-5-yl-methyl)aminocarbonylmethyl)-2-(4-fluorobenzyl)thio-5,6-trimethylenepyrimidin-4-one;

5 1-(N-methyl-N-(2-(4-chlorophenyl)benzyl)aminocarbonylmethyl)-2-(4-fluorobenzyl)thio-5-(2-aminoethyl)pyrimidin-4-one;

1-(N-methyl-N-(2-(4-chlorophenyl)benzyl)aminocarbonylmethyl)-2-(4-fluorobenzyl)thio-5-(2-acetamidoethyl)pyrimidin-4-one;

1-(N-(2-(diethylamino)ethyl)-N-(2-(4-chlorophenyl)benzyl)aminocarbonylmethyl)-2-(4-fluorobenzyl)thio-5-(dimethylaminomethyl)pyrimidin-4-one;

10 1-(N-(2-(diethylamino)ethyl)-N-(4-(4-chlorophenyl)benzyl)aminocarbonylmethyl)-2-(4-fluorobenzyl)thio-5-methylpyrimidin-4-one;

1-(N-methyl-N-(2-(4-trifluoromethylphenyl)pyrid-5-ylmethyl)aminocarbonylmethyl)-2-(4-fluorobenzyl)thio-5-methylpyrimidin-4-one;

15 1-(N-(2-(diethylamino)ethyl)-N-(4-(4-trifluoromethylphenyl)benzyl)aminocarbonylmethyl)-2-(4-fluorobenzyl)thio-5-methylpyrimidin-4-one;

1-(N-(2-(diethylamino)ethyl)-N-(2-(4-trifluoromethylphenyl)pyrid-5-yl-methyl)-aminocarbonylmethyl)-2-(4-fluorobenzyl)thio-5-methylpyrimidin-4-one;

1-(N-(2-(diethylamino)ethyl)-N-(2-(4-chlorophenyl)pyrimid-5-yl-methyl)-aminocarbonylmethyl)-2-(4-fluorobenzyl)thio-5-methylpyrimidin-4-one;

20 1-(N-(2-(diethylamino)ethyl)-N-(2-(4-trifluoromethylphenyl)pyrimid-5-yl-methyl)aminocarbonylmethyl)-2-(4-fluorobenzyl)thio-5-methylpyrimidin-4-one;

(±)-1-(N-(2-(diethylamino)ethyl)-N-(1-(4-(4-chlorophenyl)phenyl)ethyl)-aminocarbonylmethyl)-2-(4-fluorobenzyl)thio-5-methylpyrimidin-4-one;

25 1-(N-(2-(1-piperidino)ethyl)-N-(4-(4-trifluoromethylphenyl)benzyl)aminocarbonylmethyl)-2-(4-fluorobenzyl)thio-5-methylpyrimidin-4-one;

1-(N-methyl-N-(4-(4-trifluoromethylphenyl)benzyl)aminocarbonylmethyl)-2-(4-fluorobenzyl)thio-5-ethylpyrimidin-4-one

1-(N-(2-(diethylamino)ethyl)-N-(4-(4-chlorophenyl)benzyl)aminocarbonylmethyl)-2-(4-fluorobenzyl)thio-5-ethylpyrimidin-4-one;

30 1-(N-methyl-N-(2-(4-trifluoromethylphenyl)pyrid-5-yl-methyl)-aminocarbonylmethyl)-2-(4-fluorobenzyl)thio-5-ethylpyrimidin-4-one;



- 1-(N-(2-(diethylamino)ethyl)-N-(2-(4-chlorophenyl)pyrimid-5-ylmethyl)-aminocarbonylmethyl)-2-(4-fluorobenzyl)thio-5-ethylpyrimidin-4-one;
- 1-(N-(2-(diethylamino)ethyl)-N-(2-(4-trifluoromethylphenyl)pyrimid-5-ylmethyl)aminocarbonylmethyl)-2-(4-fluorobenzyl)thio-5-ethylpyrimidin-4-one;
- 5 1-(N-(2-(diethylamino)ethyl)-N-(4-(4-chlorophenyl)benzyl)aminocarbonylmethyl)-2-(4-fluorobenzyl)thio-5-propylpyrimidin-4-one;
- 1-(N-(2-(diethylamino)ethyl)-N-(4-(4-trifluoromethylphenyl)benzyl)aminocarbonylmethyl)-2-(4-fluorobenzyl)thio-5-propylpyrimidin-4-one;
- 10 1-(N-(2-(diethylamino)ethyl)-N-(4-(4-trifluoromethylphenyl)benzyl)aminocarbonylmethyl)-2-(4-fluorobenzyl)thio-5-ethoxycarbonylmethylpyrimidin-4-one;
- 1-(N-(2-(diethylamino)ethyl)-N-(4-(4-trifluoromethylphenyl)benzyl)aminocarbonylmethyl)-2-(4-fluorobenzyl)thio-5-isopropoxycarbonylmethylpyrimidin-4-one;
- 15 1-(N-(2-(diethylamino)ethyl)-N-(4-(4-chlorophenyl)benzyl)aminocarbonylmethyl)-2-(4-fluorobenzyl)thio-5-hydroxymethylpyrimidin-4-one;
- 1-(N-(2-(diethylamino)ethyl)-N-(4-(4-trifluoromethylphenyl)benzyl)aminocarbonylmethyl)-2-(4-fluorobenzyl)thio-5-hydroxymethylpyrimidin-4-one;
- 20 1-(N-methyl-N-(4-(4-chlorophenyl)benzyl)aminocarbonylmethyl)-2-(4-fluorobenzyl)thio-5-(2-hydroxyethyl)pyrimidin-4-one;
- 1-(N-(2-(diethylamino)ethyl)-N-(4-(4-chlorophenyl)benzyl)aminocarbonylmethyl)-2-(4-fluorobenzyl)thio-5-(2-hydroxyethyl)pyrimidin-4-one;
- 25 1-(N-(2-(diethylamino)ethyl)-N-(2-(4-trifluoromethylphenyl)pyrid-5-ylmethyl)aminocarbonylmethyl)-2-(4-fluorobenzyl)thio-5-(2-hydroxyethyl)pyrimidin-4-one;
- 1-(N-(2-(diethylamino)ethyl)-N-(4-(4-trifluoromethylphenyl)benzyl)aminocarbonylmethyl)-2-(4-fluorobenzyl)thio-5-(2-hydroxyethyl)pyrimidin-4-one;
- 30 1-(N-(2-(diethylamino)ethyl)-N-(4-(4-trifluoromethylphenyl)benzyl)aminocarbonylmethyl)-2-(4-fluorobenzyl)thio-5,6-dimethylpyrimidin-4-one;
- 1-(N-(2-(diethylamino)ethyl)-N-(4-(4-chlorophenyl)benzyl)aminocarbonylmethyl)-2-(4-fluorobenzyl)thio-5,6-trimethylenepyrimidin-4-one;

- 1-(N-(2-(diethylamino)ethyl)-N-(4-(4-chlorophenyl)benzyl)aminocarbonylmethyl)-2-(4-fluorobenzyl)thio-5,6-tetramethylenepyrimidin-4-one;
- 1-(N-(2-(diethylamino)ethyl)-N-(4-(4-trifluoromethylphenyl)benzyl)aminocarbonylmethyl)-2-(4-fluorobenzyl)thio-5,6-tetramethylenepyrimidin-4-one;
- 5 1-(N-(2-(diethylamino)ethyl)-N-(2-(4-trifluoromethylphenyl)pyrid-5-ylmethyl)aminocarbonylmethyl)-2-(4-fluorobenzyl)thio-5,6-tetramethylenepyrimidin-4-one;
- 1-(N-(2-(diethylamino)ethyl)-N-(4-(4-trifluoromethylphenyl)benzyl)aminocarbonylmethyl)-2-(4-fluorobenzyl)thio-5-chloropyrimidin-4-one;
- 10 1-(N-(2-(diethylamino)ethyl)-N-(4-(4-chlorophenyl)benzyl)aminocarbonylmethyl)-2-(4-fluorobenzyl)thio-5-chloropyrimidin-4-one;
- 1-(N-(2-(diethylamino)ethyl)-N-(2-(4-trifluoromethylphenyl)pyrid-5-ylmethyl)aminocarbonylmethyl)-2-(4-fluorobenzyl)thio-5-chloropyrimidin-4-one;
- 1-(N-(2-(diethylamino)ethyl)-N-(4-(4-trifluoromethylphenyl)benzyl)aminocarbonylmethyl)-2-(4-fluorobenzyl)thio-5-bromopyrimidin-4-one;
- 15 1-(N-(2-(diethylamino)ethyl)-N-(4-(4-chlorophenyl)benzyl)aminocarbonylmethyl)-2-(4-fluorobenzyl)thio-5-bromopyrimidin-4-one;
- 1-(N-(2-(diethylamino)ethyl)-N-(4-(4-trifluoromethylphenyl)benzyl)aminocarbonylmethyl)-2-(4-fluorobenzyl)thio-5-methoxypyrimidin-4-one;
- 20 1-(N-(2-(diethylamino)ethyl)-N-(2-(4-trifluoromethylphenyl)pyrid-5-ylmethyl)aminocarbonylmethyl)-2-(4-fluorobenzyl)thio-5-methoxypyrimidin-4-one;
- 1-(N-(2-(diethylamino)ethyl)-N-(4-(4-trifluoromethylphenyl)benzyl)aminocarbonylmethyl)-2-(4-fluorobenzyl)thio-5-ethoxypyrimidin-4-one;
- 25 1-(N-(2-(diethylamino)ethyl)-N-(2-(4-trifluoromethylphenyl)pyrid-5-ylmethyl)aminocarbonylmethyl)-2-(4-fluorobenzyl)thio-5-ethoxypyrimidin-4-one;
- 1-(N-(2-(diethylamino)ethyl)-N-(2-(4-trifluoromethylphenyl)pyrid-5-ylmethyl)aminocarbonylmethyl)-2-(4-fluorobenzyl)thio-5-methylthiopyrimidin-4-one;
- 1-(N-(2-(diethylamino)ethyl)-N-(4-(4-trifluoromethylphenyl)benzyl)aminocarbonylmethyl)-2-(4-fluorobenzyl)thio-5-methylthiopyrimidin-4-one;
- 30 1-(N-(2-(diethylamino)ethyl)-N-(4-(4-trifluoromethylphenyl)benzyl)aminocarbonylmethyl)-2-(4-fluorobenzyl)thio-5-methylsulfinylpyrimidin-4-one;

1-(N-(2-(diethylamino)ethyl)-N-(2-(4-trifluoromethylphenyl)pyrid-5-yl-methyl)aminocarbonylmethyl)-2-(4-fluorobenzyl)thio-5-methylsulfinylpyrimidin-4-one;

1-(N-(2-(diethylamino)ethyl)-N-(4-(4-trifluoromethylphenyl)benzyl)-aminocarbonylmethyl)-2-(2,3-difluorobenzyl)thio-5,6-trimethylenepyrimidin-4-one;

1-(N-(2-(diethylamino)ethyl)-N-(4-(4-trifluoromethylphenyl)benzyl)aminocarbonylmethyl)-2-(3,4-difluorobenzyl)thio-5,6-trimethylenepyrimidin-4-one;

1-(N-(2-(diethylamino)ethyl)-N-(4-(4-trifluoromethylphenyl)benzyl)aminocarbonylmethyl)-2-(2,3,4-trifluorobenzyl)thio-5,6-trimethylenepyrimidin-4-one;

10 1-(N-(2-(diethylamino)ethyl)-N-(4-(4-trifluoromethylphenyl)benzyl)aminocarbonylmethyl)-2-(2-fluorobenzyl)thio-5,6-trimethylenepyrimidin-4-one;

1-(N-methyl-N-(4-(4-trifluoromethylphenyl)benzyl)aminocarbonylmethyl)-2-(4-fluorobenzyl)thio-5,6-trimethylenepyrimidin-4-one;

15 1-(N-(2-(1-piperidino)ethyl)-N-(4-(4-trifluoromethylphenyl)benzyl)aminocarbonylmethyl)-2-(4-fluorobenzyl)thio-5,6-trimethylenepyrimidin-4-one;

1-(N-(2-(diethylamino)ethyl)-N-(3-(4-trifluoromethylphenoxy)benzyl)-aminocarbonylmethyl)-2-(4-fluorobenzyl)thio-5,6-trimethylenepyrimidin-4-one;

1-(N-(2-(diethylamino)ethyl)-N-(4-(4-trifluoromethylphenoxy)benzyl)-aminocarbonylmethyl)-2-(4-fluorobenzyl)thio-5,6-trimethylenepyrimidin-4-one;

20 1-(N-(2-(diethylamino)ethyl)-N-(4-(4-trifluoromethylbiphenyl-4-yl)propyl)-aminocarbonylmethyl)-2-(4-fluorobenzyl)thio-5,6-trimethylenepyrimidin-4-one;

1-(N-(2-(diethylamino)ethyl)-N-(4-(4-trifluoromethylbiphenyl-4-yl)propyl)-aminocarbonylmethyl)-2-(4-fluorobenzyl)thio-5-ethylpyrimidin-4-one;

25 1-(N-(2-(diethylamino)ethyl)-N-(4-(4-trifluoromethylbiphenyl-4-yl)oxy)ethyl)aminocarbonylmethyl)-2-(4-fluorobenzyl)thio-5-ethylpyrimidin-4-one;

1-(N-(1-ethylpiperidin-4-yl)-N-(4-(4-trifluoromethylphenyl)benzyl)aminocarbonylmethyl)-2-(4-fluorobenzyl)thio-5,6-trimethylenepyrimidin-4-one;

1-(N-(2-ethylamino-2-methylpropyl)-N-(4-(4-trifluoromethylphenyl)benzyl)-aminocarbonylmethyl)-2-(4-fluorobenzyl)thio-5,6-trimethylenepyrimidin-4-one;

30 N-(2-tert-butylaminoethyl)-N-(4-(4-trifluoromethylphenyl)benzyl)aminocarbonylmethyl)-2-(4-fluorobenzyl)thio-5,6-trimethylenepyrimidin-4-one;

N-(2-diethylaminoethyl)-2-[2-(4-fluorobenzylthio)-4-oxo-4*H*-thieno[3,2-*d*]pyrimidin-1-yl]-N-(4'-trifluoromethylbiphenyl-4-ylmethyl)acetamide;

N-(2-diethylaminoethyl)-2-[2-(4-fluorobenzylthio)-4-oxo-4 *H*-quinazolin-1-yl]-N-(4'-trifluoromethylbiphenyl-4-ylmethyl)acetamide;

5 ethyl-{2-[[2-(4-fluorobenzylthio)-4-oxo-4,5,6,7-tetrahydrocyclopentapyrimidin-1-yl]ethanoyl]-{4'-trifluoromethylbiphenyl-4-ylmethyl)amino]ethyl}carbamic acid tert-butyl ester;

1-(N-(1-methylpiperidin-4-yl)-N-(4-(4-trifluoromethylphenyl)benzyl)-aminocarbonylmethyl)-2-(4-fluorobenzyl)thio-5,6-trimethylenepyrimidin-4-one;

10 1-(N-(1-isopropylpiperidin-4-yl)-N-(4-(4-trifluoromethylphenyl)benzyl)-aminocarbonylmethyl)-2-(4-fluorobenzyl)thio-5,6-trimethylenepyrimidin-4-one;

1-(N-(1-(2-methoxyethyl)piperidin-4-yl)-N-(4-(4-trifluoromethylphenyl)benzyl)aminocarbonylmethyl)-2-(4-fluorobenzyl)thio-5,6-trimethylenepyrimidin-4-one;

15 1-(N-(2-(diethylamino)ethyl)-N-(4-(4-trifluoromethylphenyl)benzyl)aminocarbonylmethyl)-2-(4-fluorobenzyl)thio-5-(2-aminoethyl)pyrimidin-4-one; 1-(N-(2-(diethylamino)ethyl)-N-(4-(4-trifluoromethylphenyl)benzyl)aminocarbonylmethyl)-2-(4-fluorobenzyl)thio-5-(2-acetamidoethyl)pyrimidin-4-one;

20 1-(N-(2-(diethylamino)ethyl)-N-(4-(4-trifluoromethylphenyl)benzyl)aminocarbonylmethyl)-2-(4-fluorobenzyl)thio-5-(2-methanesulfonamidoethyl)pyrimidin-4-one;

1-(N-(2-(diethylamino)ethyl)-N-(4-(4-trifluoromethylphenyl)benzyl)aminocarbonylmethyl)-2-(4-fluorobenzyl)thio-5-(2-(methoxyacetamido)ethyl)pyrimidin-4-one; or

25 1-(N-(2-(ethylamino)ethyl)-N-(4-(4-trifluoromethylphenyl)benzyl)-aminocarbonylmethyl)-2-(4-fluorobenzyl)thio-5,6-trimethylenepyrimidin-4-one; or a pharmaceutically acceptable salt thereof.

20. A compound as claimed in claim 1 which is:

30 1-(N-(2-(diethylamino)ethyl)-N-(4-(4-trifluoromethylphenyl)benzyl)-aminocarbonylmethyl)-2-(4-fluorobenzyl)thio-5-ethylpyrimidin-4-one;

1-(N-(2-(diethylamino)ethyl)-N-(2-(4-trifluoromethylphenyl)pyrid-5-ylmethyl)aminocarbonylmethyl)-2-(4-fluorobenzyl)thio-5-ethylpyrimidin-4-one;

1-(N-(2-(diethylamino)ethyl)-N-(4-(4-trifluoromethylphenyl)benzyl)-aminocarbonylmethyl)-2-(4-fluorobenzyl)thio-5,6-trimethylenepyrimidin-4-one;

1-(N-(2-(diethylamino)ethyl)-N-(2-(4-trifluoromethylphenyl)pyridin-5-ylmethyl)aminocarbonylmethyl)-2-(4-fluorobenzyl)thio-5,6-trimethylenepyrimidin-4-one; or

1-(N-(2-(diethylamino)ethyl)-N-(2-(4-trifluoromethylphenyl)pyrimidin-5-ylmethyl)aminocarbonylmethyl)-2-(4-fluorobenzyl)thio-5,6-trimethylenepyrimidin-4-one;

or a pharmaceutically acceptable salt thereof.

21. A compound as claimed in claim 1 which is 1-(N-(2-(diethylamino)ethyl)-N-(4-(4-trifluoromethylphenyl)benzyl)aminocarbonylmethyl)-2-(4-fluorobenzyl)thio-5,6-trimethylenepyrimidin-4-one, or a pharmaceutically acceptable salt thereof.

22. A pharmaceutical composition comprising a compound of formula (I) as claimed in claim 1 and a pharmaceutically acceptable carrier.

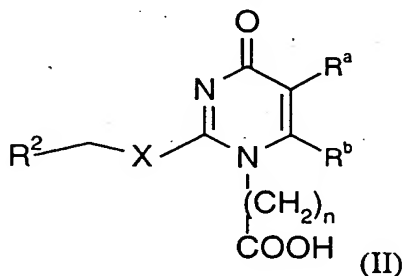
23. A method for the primary and secondary prevention of acute coronary events which method comprises administering a therapeutically effective amount of a compound of formula (I) as claimed in claim 1 to a patient in need thereof.

24. The method as claimed in claim 23 wherein the coronary event is caused by atherosclerosis.

25. A method of treating a disease state associated with activity of the enzyme Lp-PLA<sub>2</sub> which method involves treating a patient in need thereof with a therapeutically effective amount of a compound of formula (I) as claimed in claim 1.

26. A process for preparing a compound of formula (I) which process comprises:

(a) reacting a compound of formula (II):



in which

$R^a$  is hydrogen, halogen,  $C_{(1-3)}$ alkyl,  $C_{(1-3)}$ alkoxy, hydroxy $C_{(1-3)}$ alkyl,  $C_{(1-3)}$ alkylthio,  $C_{(1-3)}$ alkylsulphinyl, amino $C_{(1-3)}$ alkyl, mono- or di- $C_{(1-3)}$ alkylamino $C_{(1-3)}$ alkyl,  $C_{(1-3)}$ alkylcarbonylamino $C_{(1-3)}$ alkyl,   
 5  $C_{(1-3)}$ alkoxy $C_{(1-3)}$ alkylcarbonylamino $C_{(1-3)}$ alkyl,  $C_{(1-3)}$ alkylsulphonylamino $C_{(1-3)}$ alkyl,  $C_{(1-3)}$ alkylcarboxy, or  $C_{(1-3)}$ alkylcarboxy $C_{(1-3)}$ alkyl;

$R^b$  is hydrogen, halogen,  $C_{(1-3)}$ alkyl, or hydroxy $C_{(1-3)}$ alkyl, with the proviso that  $R^a$  and  $R^b$  are not simultaneously each hydrogen; or

10  $R^a$  and  $R^b$  together are  $(CH_2)_n$  where  $n$  is 3 or 4, to form, with the pyrimidine ring carbon atoms to which they are attached a fused 5- or 6-membered carbocyclic ring; or

$R^a$  and  $R^b$  together with the pyrimidine ring carbon atoms to which they are attached form a fused benzo or heteroaryl ring unsubstituted or substituted by 1, 2, 3   
 15 or 4 substituents which may be the same or different selected from the group consisting of halogen,  $C_{(1-4)}$ alkyl, cyano,  $C_{(1-4)}$ alkoxy or  $C_{(1-4)}$ alkylthio, and mono to perfluoro- $C_{(1-4)}$ alkyl);

$R^2$  is an aryl or heteroaryl group unsubstituted or substituted by 1, 2, 3 or 4 substituents which may be the same or different selected from the group consisting   
 20 of  $C_{(1-18)}$ alkyl,  $C_{(1-18)}$ alkoxy,  $C_{(1-18)}$ alkylthio, aryl $C_{(1-18)}$ alkoxy, hydroxy, halogen, CN,  $COR^6$ , carboxy,  $COOR^6$ ,  $NR^6COR^7$ ,  $CONR^8R^9$ ,  $SO_2NR^8R^9$ ,  $NR^6SO_2R^7$ ,  $NR^8R^9$ , mono to perfluoro- $C_{(1-4)}$ alkyl, mono to perfluoro- $C_{(1-4)}$ alkoxyaryl, and aryl $C_{(1-4)}$ alkyl;

$R^6$  and  $R^7$  are independently hydrogen or  $C_{(1-20)}$ alkyl;

25  $R^8$  and  $R^9$  may be the same or different and are selected from the group consisting of hydrogen and  $C_{(1-12)}$ alkyl; or

$R^8$  and  $R^9$  together with the nitrogen to which they are attached form a 5- to 7 membered ring optionally containing one or more further heteroatoms selected from the group consisting of oxygen, nitrogen and sulphur, and is unsubstituted or   
 30 substituted by one or two substituents selected from the group consisting of hydroxy, oxo,  $C_{(1-4)}$ alkyl,  $C_{(1-4)}$ alkylCO, aryl, or aralkyl; or

$R^8$  and  $R^9$  may be the same or different and are selected from the group consisting of  $CH_2R^{10}$  and  $CHR^{11}CO_2H$  or a salt thereof;

$R^{10}$  is  $COOH$  or a salt thereof,  $COOR^{12}$ ,  $CONR^6R^7$ ,  $CN$ ,  $CH_2OH$  or  $CH_2OR^6$ ;

- 5  $R^{11}$  is an amino acid side chain;  
 $n$  is 1 to 4; and  
 $X$  is O or S;  
 with a compound of formula (III):

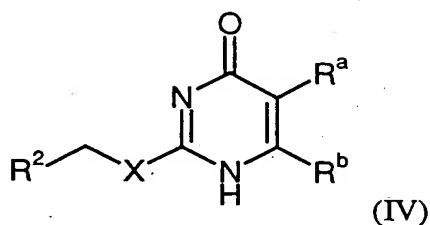


in which  $R^c$ ,  $R^3$ ,  $R^4$ ,  $R^5$ , are as hereinbefore defined;

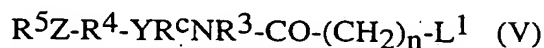
$Y$  is  $(CH_2)_p(O)_q$  in which  $p$  is 1, 2 or 3 and  $q$  is 0 or  $p$  is 2 or 3 and  $q$  is 1;

and

- 15  $Z$  is O or a bond;  
 under amide forming conditions;  
 (b) reacting a compound of formula (IV):

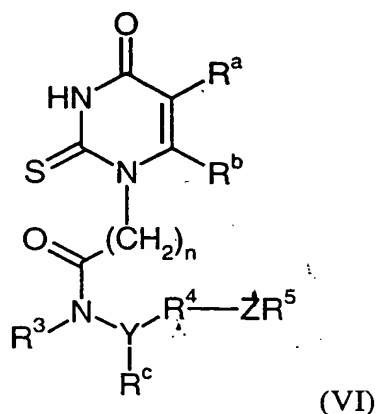


- 20 in which  $X$ ,  $R^a$ ,  $R^b$  and  $R^2$  are as hereinbefore defined,  
 with a compound of formula (V):



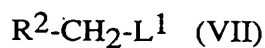
- 25 in which  $n$ ,  $R^3$ ,  $R^4$ ,  $R^5$ ,  $R^c$ ,  $Y$  and  $Z$  are as hereinbefore defined, and  $L^1$  is a leaving group such as halogen, for instance bromo iodo, or triflate in the presence of a base such as a secondary or tertiary amine in an inert solvent such as dichloromethane;

(c) when X is S, reacting a compound of formula (VI):



in which n, R<sup>a</sup>, R<sup>b</sup>, R<sup>c</sup>, R<sup>3</sup>, R<sup>4</sup>, R<sup>5</sup>, Y and Z are as hereinbefore defined,

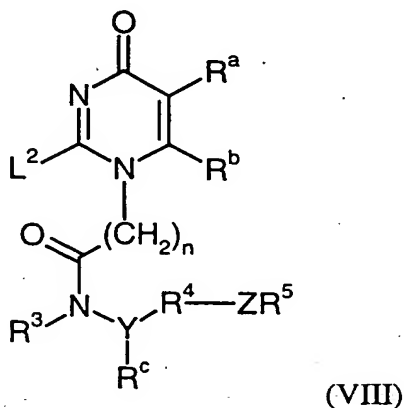
5 with a compound of formula (VII):



in which R<sup>2</sup> and L<sup>1</sup> are as hereinbefore defined,

10 in the presence of a base such as a secondary or tertiary amine in an inert solvent;

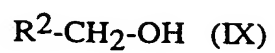
(d) when X is O, reacting a compound of formula (VIII):



15 in which n, R<sup>a</sup>, R<sup>b</sup>, R<sup>c</sup>, R<sup>3</sup>, R<sup>4</sup>, R<sup>5</sup>, Y and Z are as hereinbefore defined, and L<sup>2</sup> is a leaving group such as halogen or alkylthio,

with a compound of formula (IX):





in which  $\text{R}^2$  is as hereinbefore defined, in the presence of a base, in an inert solvent.